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KLİNİK ÇALIŞMA
RESEARCH ARTICLE

Diagnostic yield of conventional transbronchial needle aspiration biopsy (C-TBNA) without an on-site cytopathologist: Experience of 363 procedures in 219 patients

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SUMMARY

Diagnostic yield of conventional transbronchial needle aspiration biopsy (C-TBNA) without an on-site cytopathologist: Experience of 363 procedures in 219 patients

Introduction: Conventional transbronchial needle aspiration biopsy (C-TBNA) is a technique in evaluating mediastinal/hilar lymph nodes (LN). We aimed to investigate diagnostic yield (DY) and safety of C-TBNAs performed in a single university clinic.

Patients and Methods: We retrospectively reviewed 363 consecutive C-TBNA procedures in 219 patients. The DY and its relationship with location, shortest diameter, SUVmax of LN, and number of sampled stations were evaluated.

Results: Procedures were diagnostic in 257 (71%) LNs. The most common diagnoses were malignancy (n= 109, 30%) and granulomatous inflammation (n= 68, 18.7%). The ratio of patients with at least one diagnostic cytology result was 77% (n= 168). DY was significantly increased with the increased number of sampled LNs (p= 0.033) and larger LN diameter (p< 0.001). Sensitivity, specificity, positive, and negative predictive values were 83.3%, 43.2%, 79.6%, and 49.3% respectively for cut-off LN diameter of 11.5 mm. There was nearly a significant relationship between DY and SUVmax (p= 0.05, cut-off= 4.8). The highest DY was in subcarinal LN (77.4%). No major complications were recorded.

Conclusion: The DY of C-TBNA was 71%. The ratio of the patients with at least one diagnostic cytology result was 77%. The most common diagnoses were malignancy and granulomatous inflammation. The DY of C-TBNA was increased with the increased number of sampled LNs, larger LN diameter, and increased SUVmax. C-TBNA is a safe procedure.

Key words: C-TBNA, mediastinum, lymph nodes, malignancy, granulomatous inflammation

ÖZET

Konvansiyonel transbronşiyal iğne aspirasyon biyopsisinin (K-TBİA) tanısal değeri: 219 hastada 363 işlemin deneyimi

Giriş: Konvansiyonel transbronşiyal iğne aspirasyon biyopsisi (K-TBİA), mediastinal/hiler lenf nodlarının (LN) değerlendirilmesinde kullanılan bir tekniktir. Bu çalışmada bir üniversite kliniğinde yapılan K-TBİA'ların tanısal değeri ve güvenilirliğinin araştırılması amaçlandı.

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Hastalar ve Metod: Çalışmada 219 hastaya yapılan ardışık 363 K-TBİA işlemi retrospektif olarak incelendi. Tanısal başarının lokalizasyon, en kısa çap, SUVmaks değeri ve örneklenen istasyon sayısı ile ilişkisi değerlendirildi.

Bulgular: İki yüz elli yedi (%71) LN'de işlem tanısaldı. En sık tanılar malignite (n= 109, %30) ve granülatöz inflamasyonda (n= 68, %18.7). En az bir tanısal sitoloji sonucu olan hasta oranı %77 (n= 168) idi. Örneklenen lenf nodlarının sayısı (p= 0.033) ve çapı (p< 0.001) arttıkça tanısal başarı anlamlı şekilde artmaktaydı. Lenf nodu çapı 11.5 mm ve üzerinde olduğunda tanısal duyarlılık, özgüllük, pozitif ve negatif prediktif değerler sırasıyla %83.3, %43.2, %79.6 ve %49.3 bulundu. Tanısal başarı ve SUVmaks arasında sınırdan anlamlı istatistiksel ilişki mevcuttu (p= 0.05, cut-off= 4.8). En yüksek tanı başarısı subkarinal lenf nodunda elde edildi (%77.4). Hiçbir majör komplikasyon saptanmadı.

Sonuç: K-TBİA'nın tanısal başarısı %71 olarak bulundu. En az bir tanısal sitoloji sonucu olarak tanı alan hasta yüzdesi %77 idi. En sık konan tanılar malignite ve granülatöz inflamasyonda. Örneklenen LN sayısı, LN çapı ve SUVmaks değeri arttıkça K-TBİA tanı başarısı artmaktaydı. K-TBİA güvenli bir tanısal yöntemdir.

Anahtar kelimeler: K-TBİA, mediasten, lenf nodu, malignansi, granülatöz inflamasyon

INTRODUCTION

Transbronchial needle aspiration (TBNA) is a minimally invasive technique for lymph node (LN) sampling to investigate etiologies of mediastinal and hilar LNs. Although TBNA was firstly described in 1949, fiberoptic bronchoscopic application was defined in 1981 (1,2). Besides conventional usage with white light bronchoscopy (C-TBNA), its bronchoscopic appliance can also be guided by newer imaging methods like endobronchial ultrasound (EBUS-TBNA).

Conventional TBNA is a minimally invasive, safe, and cost-effective technique in evaluating mediastinal and enlarged LNs. Emergence and increasing use of EBUS-TBNA provided more information about this newer technique's diagnostic success and gave the opportunity to compare it with that of C-TBNA. The meta-analyses performed for the 3rd edition of American College of Chest Physicians (ACCP) Diagnosis and Management of Lung Cancer Guideline yielded mean pooled sensitivities of 78% and 89% for C-TBNA and EBUS-TBNA, respectively (3). There are randomized trials with results suggesting better diagnostic results with EBUS-TBNA in both lung cancer and sarcoidosis patients (4-6). Despite better diagnostic results of TBNA with additional imaging, requirement for advanced devices, special equipment and experienced staff for the specific procedure makes wide range application of those techniques uneasy (7). Thus, C-TBNA may still be important for LN sampling in terms of feasibility and practicality. Herein we report the diagnostic yield (DY) and safety of C-TBNA performed in a single center at a university clinic.

PATIENTS and METHODS

Patients

The study included 363 consecutively performed C-TBNA procedures in 219 patients who underwent

fiberoptic bronchoscopy and C-TBNA in the Bronchoscopy Unit of Hacettepe University Adult Hospital between October 1st, 2012 and December 31st, 2014. With the retrospective design, the study was approved by Hacettepe University Non-interventional Clinical Researches Ethical Committee. The files of the patients were reviewed retrospectively and available study forms were duly filled in. The age, gender, radiological findings, bronchoscopic findings, sampled LN stations, complications related to procedure, cytological findings, and final diagnoses were recorded on these forms. If available, short axis diameter on computed tomography (CT) of thorax and maximum standardized uptake values (SUVmax) on integrated positron emission tomography and CT (PET/CT) were recorded for LNs that were sampled by C-TBNA.

C-TBNA Procedure

Conventional TBNAs were performed by experienced bronchoscopists and residents under their supervision. The procedures were performed with 22-gauge cytology needles of two brands: 1) Wang MW-122 of Bard-Wang, Billerica, Mass., USA, 2) Matek TBN0122 of Matek Medical, Ostim, Ankara, Turkey. Procedures were performed without an on-site cytopathologist. Although exact numbers weren't recorded, all LN stations were sampled at least three times. The aspirates were rapidly placed on a glass slide, which was then covered with a second slide, and while applying minimal continuous pressure, the slides were drawn apart. After air-drying, the smears were transported to the cytopathology unit for staining and evaluation. Air-dried slides were stained with May-Grünwald Gimsa (MGG) stain.

Cytological Assessments

All cytological samples were evaluated by a single experienced cytopathologist. If more than one station

was sampled in a patient, each station's cytological result was recorded separately. Cytological samples were considered as diagnostic if they represented a lymph node, which is characterized by the presence of abundant lymphoid cells of polymorphous appearance. Cytological results revealing malignant cells and granulomatous inflammation were considered as specifically diagnostic for a pathological process. Cytological results revealing polymorphous lymphocytes without any other findings like granulomatous inflammation or malignant cells were also considered as diagnostic, but represented a reactionary lymph node. Cytological results revealing only bronchial epithelial cells, mucus, blood elements or inadequate cytological material were considered as non-diagnostic. Such cases were already categorized as non-diagnostic with a note on cytology reports. If cytological findings revealed specific malignancy types, these results were also recorded.

Statistical Analysis

Statistical analyses were performed by using IBM SPSS for Windows Version 21.0 statistical software package. Continuous variables presented as mean ± standard deviation (minimum-maximum). Categorical variables summarized as frequencies and percentages. Normality of the continuous variables was evaluated by Shapiro Wilks test. Differences between groups according to categorical variables were determined by chi-square and Fisher's exact tests and differences between the two groups according to continuous variables were determined by Mann-Whitney-Wilcoxon test. Pearson correlation coefficient was used to show the relation between continuous

variables. ROC curve analysis was used to show the diagnostic value of TBNA for certain LN diameter cut-off values. The sensitivity (SEN), specificity (SPE), negative predictive and positive predictive values (NPV and PPV) were calculated for these cut-offs. A p value less than 0.05 described as statistically significant.

RESULTS

The study included 219 patients (male/female: 148/71, mean age: 57 ± 13.6 years). Of 363 C-TBNA procedures, sampled stations were subcarinal in 164 (45.2%), right paratracheal in 121 (33.3%), right hilar in 58 (16%), left hilar in 13 (3.6%), and left paratracheal in 7 (1.9%) (Table 1). The DY of C-TBNA was 77.4% in subcarinal, 64.5% in right paratracheal, 71.4% in left paratracheal, 67.2% in right hilar, and 61.5% in left hilar LNs. There was no statistically significant relationship between DY and sampled LN station (p= 0.12). Conventional TBNA was diagnostic in 257 (71%) and non-diagnostic in 106 (29%) LNs. The diagnoses were malignancy in 109 (30%), granulomatous inflammation in 68 (18.7%), cystic fluid aspiration in 2 (0.6%), and reactionary lymphadenopathy in 78 LNs (21.5%) (Table 2). A specific diagnostic result was obtained in 179 (49.3%) procedures totally. Of these procedures, 109 (30%) were malignancy and 70 (19.3%) were benign disorders. The procedures revealing granulomatous inflammation were compatible with sarcoidosis in 61, tuberculosis in 3, and granulomatous inflammation accompanied by malignancy in 4 procedures. In Figure 1, the CT sections and cytological examinations of three patients with the diagnoses of adenocarcinoma, squamous cell carcinoma and sarcoidosis are presented.

Table 1. Characteristics of sampled LNs

LN station	n (%)	Diagnostic yield n (%)	Diameter		SUVmax on PET/CT	
			LNs with a measured diameter n (%)	Mean ± SD (mm) (Range)	LNs with measured SUVmax n (%)	Mean ± SD (Range)
Subcarinal	164 (45.2)	127 (77.4)	146 (89)	17 ± 10.3 (5-100)	61 (37.2)	7.77 ± 3 (2.6-12)
Right paratracheal	121 (33.3)	78 (64.5)	101 (83.4)	16.1 ± 8.9 (6-51)	50 (41.3)	7.84 ± 8.8 (1-62)
Right hilar	58 (16)	39 (67.2)	38 (65.5)	17.3 ± 7.1 (7-43)	11 (18.9)	7.40 ± 4.2 (1.85-15)
Left hilar	13 (3.6)	8 (61.5)	7 (53.8)	15.6 ± 7.4 (7-30)	4 (30.7)	8.35 ± 4.2 (4-14)
Left paratracheal	7 (1.9)	5 (71.4)	5 (71.4)	17.6 ± 6.3 (12-27)	1 (14.2)	7.2
All	363 (100)	257 (71)	297 (81.8)	16.7 ± 9.3 (5-100)	127 (34.9)	7.78 ± 7 (1-62)

LN: Lymph node, SUVmax: Maximum standardized uptake value, PET/CT: Integrated positron emission tomography and computed tomography, SD: Standart deviation.

Table 2. The cytological results of C-TBNA procedures

Cytological result	n	%
Diagnostic	257	71
Malignancy	109	30
Malignant epithelial cells	31	8.5
Non-small cell lung cancer	27	7.4
Adenocarcinoma	26	7.2
Small cell lung cancer	19	5.2
Squamous cell lung cancer	3	0.8
Neuroendocrine tumor	1	0.3
Metastasis of testis tumor	1	0.3
Reactionary LNs	78	21.5
Granulomatous inflammation	68	18.7
Sarcoidosis	61	16.8
Tuberculosis	3	0.8
Accompanied by malignancy	4	1.1
Cystic fluid aspiration	2	0.6
Non-diagnostic	106	29
Total	363	100

LN: Lymph node, C-TBNA: Conventional transbronchial needle aspiration.

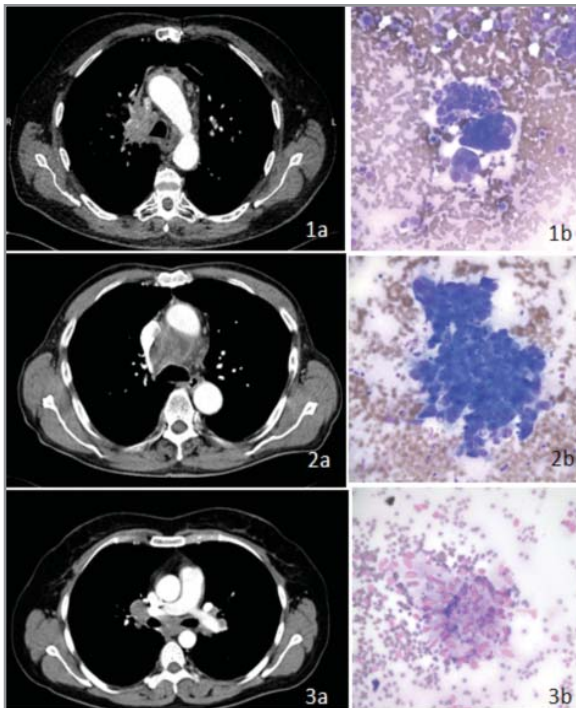


Figure 1. The CT sections and cytological examinations of three patients. Patient 1 presented with right hilar mass and right lower paratracheal LN on CT (1a), the cytology of C-TBNA revealed adenocarcinoma (1b). Patient 2 presented with mediastinal enlarged LNs on CT (2a), the cytology of C-TBNA revealed squamous cell carcinoma (2b). Patient 3 presented with right hilar and mediastinal enlarged LNs on CT (3a), the cytology of C-TBNA revealed granulomatous inflammation (3b).

Conventional TBNA provided diagnostic samples at least from one LN in 168 (77%) of 219 patients (Table 3). The number of sampled LN stations was one in 105 (47.9%), two in 84 (38.4%), and three in 30 (13.7%) patients. There was a statistically significant relationship between DY and number of sampled LN stations ($p=0.033$). Diagnostic yield was 69.5% for patients with one sampled LN station, 81% for patients with two sampled LN stations, and 91% for patients with three sampled LN stations.

Reviewing the files we reached the diameters of 297 LNs. The diameter was > 15 mm in 153 (51.5%) LNs. Mean diameter was 16.7 ± 9.4 mm (Range: 5-100). Mean diameters of diagnostic and non-diagnostic LNs was significantly different (17.7 vs 14.2 mm, $p < 0.001$). Diagnostic yield of C-TBNA according to LN diameter is presented in Table 4. Considering all LNs, a cut-off diameter of 11.5 mm or higher was suggestive to be diagnostic with a SEN, SPE, PPV, and NPV of 83.3%, 43.2%, 79.6%, and 49.3%, respectively ($p < 0.001$). The cut-off diameter was 10.5 mm for subcarinal LN with a SEN, SPE, PPV, and NPV of 90.4%, 41.9%, 85.2%, and 54.2%, respectively ($p = 0.007$). In individual analysis of remaining stations, there was no significant relationship between LN diameter and DY.

Diagnostic yield of C-TBNA according to SUVmax values are presented in Table 4. Uptake values were obtained in 127 LNs. Considering all LNs, there was a nearly statistically significant relationship between SUVmax value and DY of C-TBNA ($p = 0.05$). A cut-off value for SUVmax 4.8 or higher was suggestive to be diagnostic with a SEN, SPE, PPV, and NPV of 71.7%, 51.4%, 79.5%, and 51.4%, respectively. There was a more statistically significant relationship between SUVmax value and DY of C-TBNA at the right paratracheal region ($p = 0.035$). The cut-off value for SUVmax at the right paratracheal region was 4.9 with a SEN, SPE, PPV, and NPV of 74.2%, 63.2%, 76.7%, and 60% respectively.

Table 3. Diagnostic yields according to number of sampled LNs

Number of sampled LNs	n (%)	Diagnostic yield n (%)	p value
1	105 (48)	73 (70)	0.033
2	84 (38)	68 (81)	
3	30 (14)	27 (90)	
Total	219 (100)	168 (77)	

LN: Lymph node.

Table 4. The diagnostic yields of C-TBNA according to LN diameter and SUVmax values

Cut-off values	n (%)	Diagnostic yield n (%)	p value
Diameter (All stations)			
≤ 11.5 mm	71 (23.9)	36 (50.7)	< 0.001
> 11.5 mm	226 (76.1)	180 (79.6)	
Diameter (Subcarinal)			
≤ 10.5 mm	24 (16.4)	11 (45.8)	0.007
> 10.5 mm	122 (83.6)	104 (85.2)	
SUVmax (All stations)			
≤ 4.8	44 (34.6)	26 (59.1)	0.05
> 4.8	83 (65.4)	66 (79.5)	
SUVmax (Right paratracheal)			
≤ 4.9	20 (40)	8 (40)	0.035
> 4.9	30 (60)	23 (76.7)	

C-TBNA: Conventional transbronchial needle aspiration, LN: Lymph node, SUVmax: Maximum standardized uptake value.

Apart from minor bleeding at biopsy sites, no major complication occurred due to C-TBNA.

DISCUSSION

In this study, we retrospectively reviewed 363 consecutive C-TBNA procedures in 219 patients. The primary aim was to evaluate the DY of C-TBNA and after that to evaluate the association of DY with the location of LN, the shortest diameter, SUVmax of LN, and the number of sampled stations. We did not verify all of our results with invasive methods such as mediastinoscopy or surgery, since the primary aim was to find out the characteristics of LNs that we are capable of sampling adequately for diagnosis. For this reason cytological results revealing abundant polymorphic lymphocytes representing LN were also considered as diagnostic. It is a reality that this group might contain false negative diagnoses, since C-TBNA is just a diagnostic procedure with a low sensitivity, but 100% specificity (3). The DY of 363 procedures in 219 patients was 71%. The ratio of patients with at least one diagnostic C-TBNA procedure was 77%. While the ratio of procedures with a specific diagnosis was 49.3%, the ratio of benign reactionary LNs was 21.5%.

Conventional TBNA has been proven to be a safe, minimally invasive, and cost-effective technique for sampling mediastinal LNs. In addition to the equipment needed for bronchoscopy, TBNA needles are used. These needles are designed to pass through a bronchoscope without causing damage and are flexible enough to facilitate the positioning of the

bronchoscope, yet rigid enough to penetrate the airway wall. There are two types of TBNA needles known as flexible cytology and rigid histology needles. In a prospective study including 138 consecutive patients with bronchogenic carcinoma and amenable to surgical procedures, all 8 mm and larger mediastinal/hilar LNs determined before bronchoscopy by CT were sampled by 18-gauge rigid and 21-gauge flexible TBNAs in the same session. The sensitivities of rigid and flexible TBNAs were 74 and 70%, respectively ($p > 0.05$), but both had a specificity of 100% (8). In another study investigating the diagnostic value of 22-gauge Wang TBNA cytology needles in patients with mediastinal and/or hilar adenopathy, adequate lymph node sampling was obtained from 59 of 60 patients (98%), a specific diagnosis was obtained in 45 of 60 patients (75%) (9). In this study, we also used 22-gauge flexible cytology needles.

The DY of C-TBNA varies considerably among various studies. ACCP 2013 guideline for lung cancer found a mean pooled sensitivity of C-TBNA as 78%, ranging from 14 to 100% in terms of lung cancer (3). Studies including patients with suspicion of sarcoidosis have diagnostic sensitivities ranging from 72 to 90% (10-12). In a study including 34 patients, C-TBNA revealed a definite diagnosis in 14 patients (41.1%) and C-TBNA had a higher DY for malignancy (64.7%) compared to non-malignant diseases (17.6%) (13). Although our study included an unselected patient population in terms of suspected etiology, our DY of 71% is similar to results in the literature. The

most frequent diagnoses were malignancy followed by granulomatous inflammation. Based on these findings, we claim that C-TBNA should be considered in the diagnosis of mediastinal and hilar LNs before other more invasive procedures such as mediastinoscopy or surgery.

There are substantial amount of studies in the literature to investigate predictors of diagnostic C-TBNA. Those studies differ in terms of study designs (e.g. retrospective studies, prospective case series, and randomized controlled trials) and selected patient populations. Some of the studies include unselected patient populations whereas others include patients with specific etiologies like malignancy or sarcoidosis. Systematic review of Bonifazi et al. aiming to identify predictors successful TBNA aspirations and to define those predictors for different patient populations found LN size (≥ 2 cm for several studies), type of disease, operator experience, endoscopic findings, needle size, number of needle passes (> 3), and LN station (subcarinal and right paratracheal) as factors with strong predictive roles for unselected population (7). In another study investigating the DY of C-TBNA by size, the DY was 0% when the LN diameter was < 2 cm, 63.6% when ≥ 2 cm (13). In our study, there was no significant relationship between sampled LN station and DY. But the cut-off values 11.5 mm for all LNs and 10.5 mm for subcarinal LN were lower than 2 cm. Mean LN diameters were significantly different between diagnostic and non-diagnostic results (17.7 vs 14.2 mm, $p < 0.001$). The cut-off diameters for certain stations are important for choosing the sampling procedure EBUS-TBNA for smaller LNs, C-TBNA for larger ones.

In this study, we performed C-TBNAs from subcarinal, paratracheal, and hilar LNs. Subcarinal region was there most commonly sampled station and our best diagnostic results were achieved in there subcarinal station (77.4%). This result is probably due to two reasons. Firstly, based on technical reasons it is easy to sample subcarinal LNs. Secondly, it is important to sample subcarinal LNs for lung cancer staging as it indicates N2 disease (14). There was also a significant relationship between number of sampled LNs and DY ($p = 0.033$). This finding indicates the importance of sampling more than one station for patients with LAPs in different stations if technically available.

As an advanced imaging method, PET/CT is increasingly used for radiological staging of lung cancer. There are studies with results suggesting

increased DY of C-TBNA with higher SUVmax on PET/CT, but these studies define diverse range of SUVmax cut-offs such as 2.5, 3 and 5 (15-17). In this study, a limited percentage of patients (34.9%) had undergone PET/CT. There was a better DY with increasing SUVmax on PET/CT with a nearly significant relationship for a cut-off SUVmax 4.8.

Conventional TBNA is known as a safe procedure with a very low incidence of complications. The most common potential complications are bleeding, pneumothorax, or pneumomediastinum. Significant bleeding rarely occurs even after a major vessel puncture. Meta-analysis of Holty et al. found overall major complication rate (two major bleeds and one pneumothorax requiring chest tube) as 0.26% (18). Fever, bacteremia and hemomediastinum are other reported complications after TBNA procedures (19,20). In our study there was no major complication occurred due to C-TBNA.

Conventional TBNA has been used for over 30 years to obtain histologic and cytological specimens from mediastinal LNs with sensitivities approaching 80-90% (3). Recently EBUS-TBNA has demonstrated even higher sensitivities among experts (21,22). However EBUS-TBNA is more complicated, requires additional training, less well tolerated by patients and more costly than C-TBNA (23).

Our study's strengths include similarity of bronchoscopist experience for each procedure, analysis of both malignant and non-malignant cytologies and evaluation of cytologic samples by the same experienced cytopathologist. Retrospective basis of our study is one of the limitations. Also, results didn't include any comparison between C-TBNA results with invasive pathological sampling methods like mediastinoscopy or thoracotomy. Analyses were mainly done to evaluate sampling success, thus adequate samples without any specific diagnoses may require further diagnostic procedures. Procedure-related factors like endoscopic findings, needle brand, number of needle passes weren't analyzed. Also there wasn't any analysis based on pre-procedural suspected etiology and final diagnosis of patient.

CONCLUSION

Conventional TBNA is an effective and safe procedure for investigating both malignant and non-malignant etiologies of mediastinal and hilar LNs. Diagnostic success of procedure is increased with number of

sampled LNs, larger LN diameter (> 11.5 mm) and increased SUVmax on PET/CT. Despite its feasibility advantages, results of studies comparing EBUS-TBNA and C-TBNA favor EBUS-TBNA in terms of diagnostic yield. In current conditions, further investigations and studies may be conducted to improve EBUS-TBNA's wide range application. With decreasing trend of clinical usage of C-TBNA, it may keep its importance for settings with limited resources.

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